86-334893/51 A96 B04 D16 (B07) NIRA 27.04.85 *J6 1249-478-A

UNITIKA KK

27.04.85-JP-091613 (06.11.86) A61m-25

Anti-thrombus obturator for intra:catheter - comprises natural- or synthetic polymers and has fixed fibrinolysis activator on surface

C86-145088

B(4-B4A, 4-C2A, 4-C2B, 4-C2D, 4-C3B, 4-C3D, 11-C4B, 12-H2) 8 A(12-V3B) NO D CODES B0118

Non-thrombogenic obturator for the flow tract of an in-dwelling catheter is composed of polymers and has a fibrinolysis activator fixed on its surface.

USE/ADVANTAGE

Coagulation of the blood in an in-dwelling catheter can be avoided. The catheter can be used as soon as the obturator is removed.

MATERIALS

The obturator is composed of (a) natural polymers, such as natural rubber, cellulose, starch, collagen, agarose, dextran and proteins, or (b) synthetic polymers, such as polystyrene, polyamides, polyesters, polyamino acids, polyethylene, polyurethane, polypropylene, silicone resin, polyvinylchloride, polymethacrylate ester, polyvinyl alcohol and copolymer of ethylene and vinyl acetate.

The fibrinolysis activator fixed on the surface of the obturator may be plasmin, urokinase, streptokinase or tissue plasminogen activator.

EMBODIMENT

The diameter of this obturator is almost the same as the inside diameter of the catheter. The obturator is tubular or cylindrical with a round tip, and its length is the same as that of the catheter or a few centimeters longer.

EXAMPLE

Cylindrical obturator (0.9 mm diameter and 27 cm length) made of polyvinyl chloride was dipped in an acetone solution containing 2 wt./vol. % of copolymer of maleic acid anhydride and methylvinyl ether and 1 wt./vol. % of polyethylene glycol (molecular weight: 400) for 1 minute. The obturator was then heated at 90-100°C for 2 hours under low pressure and dipped in a physiological saline solution containing urokinase (600 U/ml) at 70°C for 24 hours.

Thus obtained obturator (2 mm of length) provided with urokinase could dissolve fibrin around it in an area of 400 mm². (4ppW45EDDwgNo0/0).

J61249478-A

C86-335071/51 A96 B07 TEIK 26.04.85 *J6 1249-914-A

TEIKOKU HORMONE MFG LTD

26.04.85-JP-088800 (07.11.86) A61k-09

Mfg. sparingly soluble drug for oral admin. - by dissolving drug and polymer in organic solvent adding insoluble power, kneading then removing solvent

C86-145257

A(12-V1) B(1-A1, 1-C2, 1-C3, 1-C5, 3-A, 3-H, 4-C2A, 4-C2A2, 4-C3B, 4-C3C, 5-A1B, 5-B2A3, 5-B2C, 6-D1, 10-B2A, 10-C3, 12-D7) B0119

Prodn. of a sparingly soluble drug prepn. involves:

(i) dissolving a sparingly soluble drug and a polymer in an organic solvent;

(ii) adding a powder which is insoluble in the organic solvent;

(iii) kneading the resulting soln.; and

(iv) removing the solvent.

USE/ADVANTAGE

When sparingly soluble drugs are administered orally, they are easily dissolved in the digestive tract.

MATERIAL

Sparingly water-soluble drugs may be:

(a) steroids, e.g. chlormadinone acetate, estrone, progesterone, methyltestosterone or hydrocortisone;

(b) anti-inflammatory drugs, e.g. flufenamic acid, indomethacin, anthranilic acid or methyl salicylate;

(c) lipophilic vitamins, e.g. vitamin A or vitamin E.

Pref. polymers are e.g. hydroxypropyl cellulose, hydroxypropylmethyl cellulose, methylcellulose, carboxymethylethyl cellulose, polyethylene glycol or glycerides.

Any organic solvent which can dissolve both drugs and polymers but not the powder can be used (e.g. dichloromethane, chloroform and methyl alcohol).

Powders used are e.g. magnesium aluminate metasilicate, aluminium silicate, silicic anhydride, aluminium hydroxide or tricalcium phosphate.

EMBODIMENT

In a standard method, the powder is added to the organic solvent contg. the drugs and the polymers and the mixt. is kneaded by a kneading machine.

The organic solvent is removed by evaporating, heat drying and spray drying. (4ppW45LGDDwgNo0/0).

J61249914-A

86-335072/51 B05 MIZU/ 26.04.85 *J6 1249-918-A

MIZUSHIMA H

26.04.85-JP-090426 (07.11.86) A61k-09/10

Eye drops - composed of lipid microspheres contg. remedies for eye troubles

C86-145258

B(12-L4, 12-M7, 12-M10A, 12-M11) 2 B0120

Eye drops which are composed of lipid microspheres (LMS) containing remedies for eye troubles are new.

USE/ADVANTAGE

The drops provide continuous absorption and action on eye tissues without side effects.

They are used several times a day, and they have no toxicity other than the side effect specific to the remedies contained in them.

THERAPEUTIC AGENT

Any remedy for eye trouble can be used, i.e. corticosteroid, cyclosporin, antibiotics, non-steroid anti-inflammatory drugs, remedies for cataract, remedies for glaucoma, etc.

PREPARATION

LMS is produced conventionally except that the remedies are added in the course of production. Soybean oil is preferred as the oil, and lecithin is preferred as the emulsifier. The oil, the emulsifier and the remedy are mixed and heated at 30-80°C. The mixture is homogenised, sterilised water is added and the mixture is homogenised again.

Thus obtained LMS has a radius of 0.1-1.0 μm and is very stable for a long time.

EXAMPLE

100 g of purified soybean oil, 25 g of purified yolk lecithin, 0.05 g of sodium oleinate and 1 g of hydrocortisone 17-butyrate 21-propionate were mixed, heated at 65-75°C and homogenised. 5 g of glycerine and 870 ml of sterilised water were added and the mixture was emulsified by homogeniser.

The obtained solution was an emulsion composed of particles of about 0.2 μm in diameter. This eye drop was demonstrated to be able to penetrate eye tissues (e.g. corne and iris) by experiment using radioisotopes. (4ppW45EDDwgNo0/0).

J61249918-A

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(54) Title of the Invention

Collyrium comprising microspheres containing ophthamic disease treating agent

(21) Patent Application No. 60-90426
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Specification

1. Title of the Invention :

Collyrium comprising microspheres containing ophthamic disease treating agent

2. Claim :

A collyrium which comprises lipid micro sphere

containing therapeutic agent for eye disease.

3. Detailed Explanation of the Invention :

[Field of the invention]

This invention relates to a collyrium.

[Background of the invention and problems to be dissolved by the invention]

Various kinds of collyriums have been conventionally used and most of them are in the form in which a therapeutic agent for eye disease is dissolved or suspended. Continuation of absorption and action to the eye tissue has been studied ; For example, water soluble polymers such as methylcellulose, polyvinyl alcohol, hydroxypropylmethylcellulose and the like are used for increase of the viscosity of collyrium. However, it is not sufficient.

Furthermore, collyrium containing adrenal cortical hormone is used for eye morbiness occured in Behcet's disease of which patients have increased recently. It can not be said that the collyrium transfers into every intraocular tissue sufficiently. Therefore, general administration and injection into eyeball should be taken together against the morbiness of the eye. As the result, the side effect of adrenal cortical hormone itself is liable to appear. Additionally, a new treatment such as oral administration of cyclosporin has been tried in the case of keratoplasty but it is also apt to provide side effects on the kidney and the like.

The present inventors have been studied to find out a collyrium having continuation of absorption and action to eye tissues which could not be achieved by the conventional collyriums but showing no side effect and finally accomplished the present invention.

[Means for dissolving the problems]

Namely, this invention relates to a collyrium consisting of lipid micro sphere (which is abbreviated as LMS

hereinafter).

Any drug generally used for treatment of eye disease can be utilized as therapeutic agent used in the collyrium of this invention. For example, they are corticosteroids (e.g. cortisone acetate, hydrocortisone acetate, prednisolone acetate, dexamethasone, sodium dexamethasone metasulfobenzoate, sodium dexamethasone sulfate, sodium dexamethasone phosphate, sodium betamethasone phosphate, fluorometholone, hydrocortisone 17-butyrate 21-propionate or their mixture); cyclosporin; antibiotics (e.g. erythromycin, erythromycin lactobionate, kanamycin sulfate, bekanamycin sulfate, gentamycin sulfate, dibekacin sulfate, tobramycin, micronomycin sulfate, tetracycline hydrochloride, oxytetracyclin hydrochloride or chloramphenicol); non-steroidal anti-inflammatories (e.g. water-soluble azulene , flurbiprofene , indomethacin, glycyrphosphoric acid or the esters); therapeutic agents for cataract (e.g. catarin, cineraria , sodium 5,12-dihydroaza-pentacene sulfonate or glutathione), therapeutic agents for glaucoma (e.g. timolol or befunolol) and the like. They may be used in single or as a mixture. Additionally, preservatives and the like may be added to the collyrium of this invention.

Process for preparing the collyrium of this invention is caried out in the usual manner for preparing LMS with addition of the above-noted therapeutic agent. For example, about 5-50 % (w/v) of oil component, about 1-50 parts by weight of emulsifier to 100 parts by weight of oil component and a suitable amount of a therapeutic agent for eye disease are mixed under using as oil component soybean oil, cotton seed oil, sesame oil, sunflower oil, corn oil, squalene, eicosapentenoic acid and the esters, azone and the like, preferably soybean oil, and as emulsifier non-ionic surfactants and phospholipids (lecithin, hydrogenated lecithin), preferably lecithin. An emul-

sifier (e.g. within 0.3 % (w/v) of C_{6-22} fatty acid), a stabilizer (e.g. within 0.5 %(w/v) of cholesterol) and an isotonic agent (e.g. glycerol) may be added thereto, if necessary. The amount of the therapeutic agent is varied depending on the kind, disease condition of a patient and the like, while the amount usually used for a collyrium is, for example, 0.005 - 2 % (v/w), preferably 0.01 - 1.2 % (w/v). Successively, the mixture is heated to 30 - 80 ℃, made homogeneous, for example, by a homogenizer and after addition of a necessary amount of a sterilized water, homogenized again, for example, with a homogenizer to give the desired product. The resulting LMS has a mean particle diameter of about 0.1 - 1.0 μ and the conservative stability is extremely good.

The collyrium of this invention is applied several times a day by dropping in the eyes.

The collyrium of this invention has no toxicity except for the specific side effect of the therapeutic agent contained.

The collyrium of this invention has been explained as collyrium thereinbefore, while eye ointments containing LMS may be also prepared according to the conventional procedure.

[Example]

Examples are shown below:

Example 1

A hundred grams of purified corn oil, 25 g of purified yolk lecithin, 0.05 g of sodium oleate and 1 g of hydrocortisone 17-butyrate 21-propionate were heated at 65 - 75 ℃ and made homogeneous by a homomixer. Successively, 5 g of glycerol and 870 ml of a sterilized water were added thereto and the mixture was emulsified by passing through a homogenizer in Manton-Gaulin type under a pressure of 120 kg/cm^2 for the first step and the total pressure of 500 kg/cm^2. The resultant product was a fine

emulsion having a particle diameter of about 0.2 μ

Example 2

A fat emulsion was prepared using eicosapentenoic acid instead of soybean oil in Example 1 for the purpose of increasing the concentration of hydrocortisone 17-butyrate 21-propionate in the fat emulsion. Namely, 10 g of eicosapentenoic acid, 1.2 g of purified yolk lecithin, 0.05 g of sodium oleate, 500 mg of hydrocortisone 17-butyrate 21-propionate and 2.5 g of glycerol were mixed and sterilized distilled water was added to adjust the total amount to 100 ml. The mixture was emulsified in the same manner as in Example 1. The resulting product has a mean particle diameter of about 0.1 μ and the conservative stability was good.

Example 3

Ten grams of purified soybean oil, 1.2 g of purified yolk lecithin and 200 mg of cyclosporin were mixed under heating of 65 - 75 C, 2.5 g of glycerol were added thereto, the total amount was adjusted to 100 ml by addition of sterilized distilled water and the mixture was emulsified in the same manner as in Example 1. The resulting product was a fine emulsion having a particle diameter of about 0.1 - 1.0 μ. The conservative stability was good and change of particle diameter was not observed.

Example 4

A fat emulsion containing erythromycin was prepared by using azone (1-dodecylhexahydro-2H-azepin-2-one) instead of soybean oil in Example 2. Namely, 10 g of azone, 1.2 g of purified yolk lecithin, 500 mg of erythromycin and 2.5 g of glycerol were mixed, the total amount was adjusted to 100 ml with sterilized distilled water and the mixture was emulsified in the same manner as in Example 1. The resulting product was a fine emulsion having a mean particle diameter of about 0.2 μ. The conservative stability was good.

[Effect]

The effect of the collyrium of this invention is shown as follows:

A collyrium containing ^{3}H labeled hydrocortisone 17-butyrate 21-propionate at a concentration of 4.6 μCi/1.4 ng/ml (noted as Collyrium A hereinafter) was prepared according to the process in Example 1.

On the other hand, ^{3}H labeled hydrocortisone 17-butyrate 21-propionate was dissolved into 0.05 % polysolbet 80 (produced by Wako Junyaku Co.) to give a suspension for eye dropping and the concentration was adjusted to 36.5 μCi/0.27 ng/ml (noted as Collyrium B hereinafter).

The concentration of the drug in the intraocular tissue after eye dropping was measured with New zealand white rabbits of 3 - 4 kg of body weight divided into two groups for dropping of collyrium A and Collyrium B into the eyes by comparing 6 eyes of each group. The dose of the collyrium was 20 μl/time. Pentobarbitone sodium was injected into the ear vein 1 and 3 hours after the eye dropping and then the eyeball was enucleated. Every intraocular tissue was separated and soaked in Soluene 350 (produced by Packert Co.) for 4 days for decomposition. After addition of 10 ml of Soluene 350, the content of ^{3}H labeled hydrocortisone 17-butyrate 21-propionate in each intraocular tissue was counted by a scintillaltion counter. The result is shown in Table 1. The figure means % value of ^{3}H content of each tissue to ^{3}H content of the total liquid volume.